Good Practice in PMA Submissions for Efficient Regulatory Decision Making

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Outline

- Highlights and impact of MDUFA III on review clock
- Frequently encountered issues with PMA submissions
- Statistical reviewers perspectives on ready-to-review PMA submissions

MDUFA III Goals : original PMA's and panel track supplements

- MDUFA III Highlights
  - Electronic copy of submissions (e-Copy)
  - Acceptance/Filing review checklists
  - Interactive review
- Goals for PMA's
  - Substantive Interaction within 90 calendar days
    - 75% of submissions in FY 2014/15 - 95% of submissions in FY 2016/17
  - Final decision within 180 days (no panel input required)
    - 80% of submissions in FY 2014/15 - 90% of submissions in FY 2016/17
  - Final decision within 320 days (panel input required)
    - 70% of submissions in FY 2014 - 90% of submissions in FY 2017

Impact of MDUFA III goals on review timelines

- Statistical reviewer has ~50 calendar days to conduct substantive review of original PMA
  - >25% reduction in review time

- Short turnaround for interactive reviews

Review time will be adversely impacted when essential information is missing or hard to locate. A comprehensive ready-to-review submission is critical for meeting MDUFA III goals.

Common Issues : Regulatory History

- Incomplete regulatory history of device
  - Discuss any prior IDE studies/PMA submissions for same/related devices
  - Provide IDE/PMA numbers of related submissions
    - Easier to query CDRH repositories by submission number
      - Referring to related devices/studies only by device/study name makes it more difficult to locate the relevant submissions

Common Issues : Study Protocol

- At a minimum provide final approved version of study protocol and SAP
  - Provide study protocol for all major revisions
  - Include SAP with protocol rather than in the appendix in a separate volume
- Provide summary of changes from one protocol version to another
  - Timeline of major protocol revisions
  - Justification for protocol revisions
    - so we can determine its potential impact on study conclusions; for example whether a major protocol revision occurred before/after enrollment began

Common Issues : Protocol Deviations

- Provide summary tables by type (major/minor) of deviation
  - Protocol deviations by investigational site
- Summarize narratives in CRFs related to major protocol deviations
  - Discuss relatedness of protocol deviations to endpoint assessments
- Discuss impact of specific deviations on study conclusions
  - Extensive deviations from approved study protocol can make it difficult to interpret study data

Common Issues : Analyze as pre-specified in IDE

- Provide all analyses pre-specified in IDE protocol
  - Not submitting analyses pre-specified in the IDE protocol will potentially result in a major deficiency letter and/or slow down review
- Applicant is free to submit supporting analyses for consideration
  - Submit pre-specified analysis first
  - Note any other analyses as post-hoc analyses
  - Justify any deviations from pre-specified analyses

Common Issues : Missing Data

- Reasons for missing data
  - Why data is missing (missed visits, outcome data not readable, value not recorded etc)
  - When data became missing
- Undisclosed data omitting
  - Justify any data omission (ex. values are outliers)
  - Clearly note if any data has been imputed
- Impact of missing data on study results
  - Compare pattern of missing data between treatment groups in terms of timing of missingness

Have a pre-specified plan for analyzing missing data!

Common Issues : Trial Data

- Include electronic datasets and analysis code in PMA submission
  - Make sure it can be easily transported to SAS if another data format is preferred
- Provide Adverse Event listings for medical reviewers
- Provide analysis dataset used for analysis of study endpoints rather than just raw data
- Provide code used to produce the tables and listings in the clinical study report

Reviews can be significantly delayed if reviewers have to write their own code to verify study results.

Common Issues : Trial Data

- Complicated manipulations required to validate results
  - Provide analysis datasets to support key effectiveness/safety analyses
    - Avoid having to merge datasets to perform analyses
  - Include code used for creating analysis datasets from raw data
  - Analysis datasets should contain basic demographic variables (ex. Sex, Age, Site etc.)and important covariates
  - Ensure no inconsistencies between various datasets

Common Issues : Trial Data

- Datasets and code often poorly documented
  - Define/README file for datasets and program files
    - explain which results table is generated by which codes and datasets
    - describe variables used for coding primary, secondary endpoints & demographic variables
    - every data variable's origin and derivation should be clearly and easily accessible from the define file
    - easy to understand how derived variables are obtained from raw dataset
- If analysis datasets contain imputed data
  - Provide supporting documentation to explain the imputation method

Common Issues : Trial Data

- Mis-packaged programs
  - Missing macros used in analysis
  - Missing Proc Format program that creates the format catalog
  - Wrong relative directory in libname references
- Ensure traceability
  - From analysis results back to the original data elements collected in CRF's
- Test-run programs to ensure they run smoothly and generate correct analysis results
  - Mock-run by another statistician not involved with study

Data Monitoring Committee (DMC) Issues

- DMC charter not provided
  - Comprehensiveness of DMC charter
  - SOP for maintaining firewalls
  - Even for open label studies only DMC should have access to unblinded summary data across all centers
- Meeting minutes not provided
  - Minutes for closed/open sessions and written reports to sponsor
  - For example, provide all DMC recommendations regarding adaptations for adaptive designs

Common Issues : Annual reports

- Unless specifically requested by FDA don't analyze effectiveness data by treatment group

- Maintain firewall between statistician responsible for performing annual report analysis and other statisticians/decision makers in the sponsor's organization

FDA – Sponsor interaction

- MDUFA III emphasizes interactive review
  - Quick turnaround required from sponsor for effective interactive review
  - Provide code for any additional analysis requested/presented during interactive review
  - Be prepared to work interactively if reviewers are unable to run code submitted by sponsor
  - Be prepared to conduct additional simulation /sensitivity analyses
    - Ex. simulations under additional scenarios for adaptive and Bayesian designs

Pre-subs can improve review efficiency

Pre-submission (Pre-Sub) in advance of PMA submission

- Strongly recommended for any PMA submission
- Opportunity for FDA to provide feedback on what is expected in PMA submission
- Gives advance information to reviewers to be prepared for PMA

Make use of the pre-submission program!

What should be in a Pre-Sub?

For the clinical study, pre-sub draft guidance recommends including

- Patient accountability chart with discussion of how missing data will be addressed in analysis
- Format of presentation of clinical study results
  - shell of tables to be included, charts, analysis populations, summaries, conclusions
- Proposed indications and how data support these
- Intended claims and data to support these claims
- Identify deviations from SAP
- Provide details of analysis code and dataset
  - will code be provided in SAS/R?
  - what datasets will be provided?

Non-standard data is a major hurdle

- Issues with data coding and presentation one of the primary reasons for delay in review
- Limits ability to ask in depth questions and address late-emerging issues in timely manner
- Increases variability in quality of reviews
- Reduces transparency and predictability

Recommendations on data submission

- Conform to data standards
- At least one analysis dataset should be labeled in the data definition file as containing the primary safety/effectiveness data
- Submit analysis code so results in study report can be verified quickly
- Provide documentation for datasets and code

Conforming to data standards like CDISC can make it easier for the FDA to review and analyze data

Summary

- Submit comprehensive PMA submission
  - Be aware that this might be the FDA reviewers very first exposure to the study
  - Try to anticipate potential questions from reviewers
- Use PMA review statistical checklist to ensure completeness
- Analyze as pre-specified
  - Pre-specify analysis population and statistical tests to be used
  - Pre-specify how missing data will be analyzed
- Be responsive to interactive review requests

References

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